## REMARKS

Claims 1-15 are pending.

Claim 1 has been amended to include lactose. Support for the amendment can be found in Examples 1, 2, 4 and 6-9.

Claims 3-5 and 11-15 have been amended to remove the phrase "and the like."

Claim 4 has also been amended to remove the phrase "and derivatives."

Claim 7 has been amended to correct a typographical error.

Claims 13 and 14 have been amended by replacing the phrase "AEROSIL® 200" with the generic description of this product, which is "fumed silica."

No new matter has been added.

Objections to the Specification

The Examiner has objected to the Specification, stating that no generic description of AEROSIL® 200 was provided and that while a generic description of KOLLICOAT® was presented, it is incomplete. The Examiner has also required the names of all trademarked products to be capitalized.

Applicants have amended the Specification to include a description of AEROSIL® 200 as "fumed silica." The Specification states on page 3, line 33, that AEROSIL® 200 is a "binding- and disintegrating-action agent." This description correlates with the generic description of AEROSIL® 200 available from suppliers, which also describe the product as "fumed silica" (see copies attached). Because the generic description that is present in the Specification, i.e. a "binding- and disintegrating-action agent," corresponds to the generic description provided by the manufacturers, expanding this generic definition in the Specification to include "fumed silica" does not introduce new matter. Therefore, Applicants request entry of the amendment and removal of the objection.

Applicants have also provided a full generic description of the KOLLICOAT® used in the Examples, which is KOLLICOAT® SR 30 D. This product is a poly (vinyl acetate) dispersion stabilized with povidone and sodium lauryl sulphate, as evidenced by the attached supplier's descriptions. There are many KOLLICOAT® products, such as KOLLICOAT® MAE, which is

the copolymer between methacrylic acid and ethyl acetate, but this product is not used in the Examples nor is it recited in the Specification. Therefore, since Applicants have merely provided the generic description of the product named and used in the Examples, Applicants request entry of the amendment and removal of the objection.

Applicants have capitalized the names of all trademarked products, thereby overcoming the rejection.

Objections to the Claims

The Examiner has objected to claim 7, noting that a space is needed between "to" and "20%" in line 2. Applicants have amended the claim, thereby overcoming the objection.

The Examiner has objected to claim 14, noting that a space is needed between "of" and "Aerosil® 200" in line 2. Applicants have amended the claim, thereby overcoming the objection.

The Examiner has objected to claim 13 noting that Aerosil® is incorrectly spelled as "Aerosite." Applicants have amended the claim, thereby overcoming the objection.

Rejections Under 35 USC § 112, First Paragraph

The Examiner has rejected claim 4 for lack of written description, stating that the reference to "derivatives" in claim 4 corresponds in some undefined way to the instantly disclosed chemicals.

Applicants have deleted the phrase "and derivatives" from claim 4, thereby overcoming the rejection.

Rejections Under 35 USC § 112, Second Paragraph

The Examiner has rejected claims 3-5 and 11-15 as indefinite for recitation of the phrase "and the like." Applicants have deleted this phrase from the claims, thereby overcoming the rejection.

Rejections Under 35 USC § 102

The Examiner has rejected claims 1-5 and 7-15 as anticipated by Maegerlein et al. as evidenced by Azarmi et al. The Examiner contends that the Maegerlein et al. reference presents a tablet for sustained release containing all of the elements required in the instant claims in the amounts recited. Applicants respectfully traverse.

Applicants have amended claim 1 to require lactose. Maegerlein et al. do not discuss lactose. Consequently, because the Maegerlein et al. reference does not contain each element of the instant claim, it cannot support a novelty rejection. Applicants therefore request removal of the rejection.

Rejections Under 35 USC § 103

The Examiner has rejected claim 6 as obvious over Maegerlein et al. as evidenced by Azarmi et al. in view of Pankhania et al. The Examiner contends that the Maegerlein et al. formulation combines torasemide with an acrylic polymer and also discloses xanthan gum and galactomannan as suitable polymers, but fails to specifically mention guar gum. The Examiner attempts to fill this void with the disclosure of Pankania et al., which she states teaches xanthan gum, guar gum and acrylic resins as polymers known for possessing sustained release properties. From this the Examiner concludes that the skilled artisan would be motivated to replace the exemplified acrylic polymer with guar gum. We assume that the Examiner means replacing the Eudragit acrylic polymer in Examples 8 and 9 of the Maegerlein et al. formulations with guar gum.

The Examiner has also rejected claims 1-15 as obvious over Berner et al. in view of Kaplan. The Examiner contends that the Berner et al. reference presents controlled release, gastric retentive dosage forms for oral administration and, while not showing a formulation containing torasemide, does list this as one of nine diuretic drugs that could be used. The Examiner also contends that this reference mentions fillers, binders and additives for tablet formulation for oral administration as well as the use of acrylic acid polymers, cellulose polymers, and guar gum as the polymer for sustained release. The Examiner admits that Berner et al. do not exemplify a formulation comprising torasemide. The Examiner then relies on

Kaplan to provide the teaching that long-acting formulations are preferred and that torasemide is a longer-acting diuretic.

Applicants respectfully traverse.

Applicants first note that the Pankhania et al. reference states that the sustained release carrier comprises a major proportion of xanthan gum. Consequently, while Pankania et al. recite guar gum as one of many polymers having sustained release properties that can replace xanthan gum, there is no suggestion that the amount of guar gum would be different from the amount of xanhan gum used in the formulation.

Applicants next point out that lactose is a well known diluent which is normally used in immediate release formulation, not in controlled release formulations since it normally does not influence or control the release profile. On the contrary, it is sometimes used as a release enhancer. Therefore, in view of the teachings in the art as a whole, a skilled artisan would not have had a reasonable expectation of success in obtaining the instantly claimed invention which has controlled release by using lactose in the formulation.

To assist the Examiner in appreciating the instant invention, Applicants make the following points. The present invention has a formulation containing torasemide, a matrix forming polymer and lactose as the main diluent. This results in a prolonged-release formulation of torasemide which shows a kinetic profile with fewer fluctuations and steadier levels. The percentage of lactose in the preferred formulations of the invention is about 50% of the blend (see examples 6-9). On the other hand, the matrix forming polymer is present in a small proportion in the formulation of the invention; normally less than 20% of the total composition, and more preferably from 2-5%.

To illustrate the kinetic profiles of examples of the torasemide formulations (tablets) of the claimed invention, Meyprogat® 90 (i.e. guar gum) at 10, 5 and 3% of the total tablet weight was tested as shown in the Table below for the 5 mg tablet dose (5 mg torasemide).

| Formulation | T1604 | T1704 | T1804 |
|---|---|---|---|
| Torasemide | 5.9 % | 5.9 % | 5.9 % |
| Corn starch | 36.2 % | 36.2 % | 36.2 % |
| Colloidal Silicon Dioxide | 0.5 % | 0.5 % | 0.5 % |
| Meyprogat® 90 | 10.0% | 5.0 % | 3.0 % |
| Magnesium stearate | 0.3 % | 0.3 % | 0.3 % |
| Lactose | 47.1% | 52.1 % | 54.1 % |

The following dissolution tests were performed with hydrochloric acid 0.1 N.

In comparison with Sutril® (Immediate release formulation), the experimental tablets showed a prolonged release behaviour starting from 3% of guar gum (batch T1804). The total release of the active in this batch (T1804) was produced in 5 hours. Batches with 5% and 10% of the excipient (i.e. T1704 and T1604) presented a 75% active release within 5 hours with a similar kinetic profile. The following table and figure show the results of the kinetic profile of these formulations.

| | Sutril 5 mg | | Batch T1604 | | Batch T1704 | | Batch T1804 | |
|---|---|---|---|---|---|---|---|---|
| Time (min) | Release per time fraction % | Release % | Release per time fraction % | Release % | Release per time fraction % | Release % | Release per time fraction % | Release % |
| 0 | - | 0 | - | 0 | - | 0 | - | 0 |
| 0.5 | 98.2 | 98.2 | 22.5 | 22.5 | 23.4 | 23.4 | 26.6 | 26.6 |
| 1 | 2.3 | 100.5 | 10.2 | 32.7 | 7.2 | 30.6 | 7.4 | 34.1 |
| 2 | 0.4 | 101.3 | 7.5 | 47.7 | 6.4 | 43.5 | 12.7 | 59.6 |
| 3 | -0.6 | 100.1 | 5.7 | 59.0 | 5.7 | 54.8 | 12.8 | 85.1 |
| 4 | -0.3 | 98.9 | 3.7 | 73.9 | 6.1 | 79.1 | 3.1 | 97.5 |

***Table.*** Release values (with HCl 0.1N) for tablets manufactured with Meyprogat® 90.

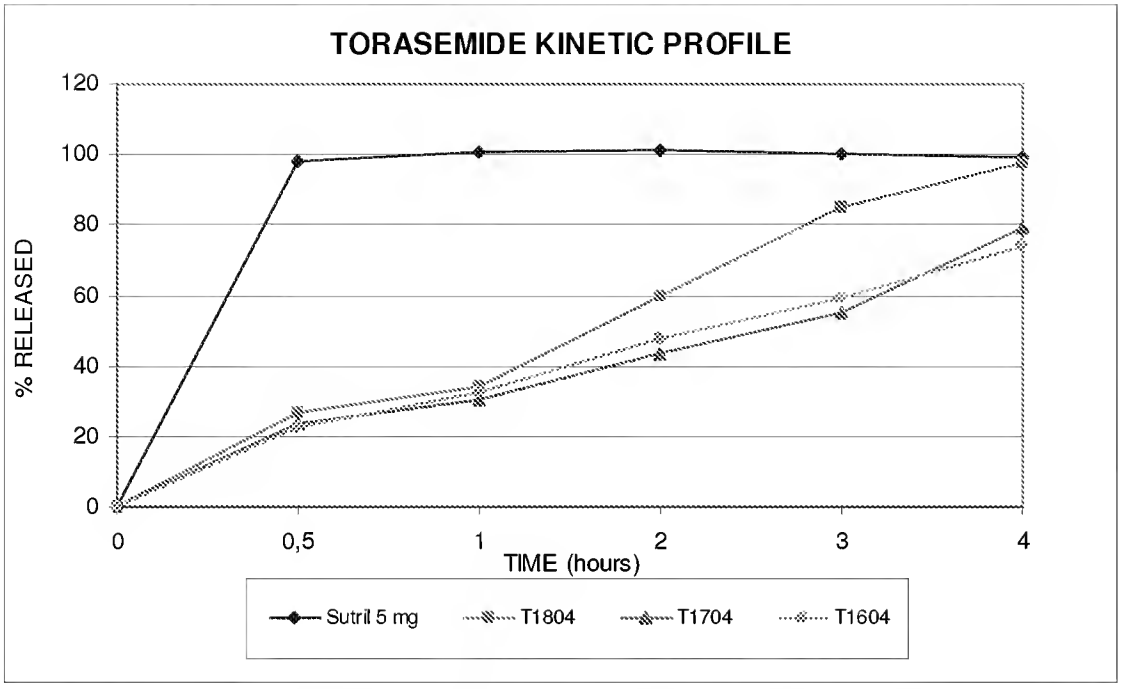


***Figure.*** *Release profiles (with HCl 0.1N) of Torasemide from Meyprogat® 90matrix tablets.*

The percentage of lactose in the experiments is above 45% with respect of the blend. The amount of guar gum is less than 10% of the amount of lactose.

Thus, in view of the above discussion, Applicants submit that the instant invention is not obvious over the cited prior art and respectfully request removal of the rejection.

Conclusion

In view of the above remarks, all of the claims are submitted as defining non-obvious, patentable subject matter. Reconsideration of the rejections and allowance of the claims are respectfully requested. Applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Susan W. Gorman, Ph.D. Reg. No.

47,604 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R §§ 1.17 and 1.136(a), Applicants respectfully petition for a two (2) month extension of time for filing a response in connection with the present application. The Commissioner is authorized to charge Deposit Account No. 02-2448 in the amount of $490.00 is for the required fee under 37 C.F.R. § 1.17 (a)(2) for an extension of time within the second month.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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Enclosures: Degussa product information AEROSIL 200®
Evonik information for AEROSIL 200 ®
ChemCrete AEROSIL 200® product description
BASF KOLLICOAR® SR 30 D
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